In the Description

At page 8, line 21, page 9, line 11 and page 9, line 14, please replace the term "L-Lp(D)$_n$" with the term "L-Lp(D)$_n$".

In the Claims

Please cancel Claims 17, 18, 26, 27, 28 and 30 (without prejudice); enter the indicated amendments to Claims 2 to 11, 13 to 16, 19 to 22, 24 and 25; and enter new Claims 31 to 35. Directions for amendment of claims are indicated on the copy of the attached hand amended ("marked up") original claims, showing in manuscript the amendments that have been made and the origins of the new claims. Clean forms of new and rewritten claims are included in the attached "Clean Set of Claims" document.

Remarks

This application seeks protection for certain novel compounds that are inhibitors of the serine protease, Factor Xa, and are useful for the treatment of thrombotic disorders. It is the national stage of an international application, the claims of which were drafted in accordance with international practice.

Applicants now wish to amend the application to bring it into conformity with United States patent practice.

For the assistance of the Examiner, a copy of the original claims is attached, as noted above, showing in manuscript the amendments that have been made.

The description at pages 8 and 9 has been brought into conformity with claims 4 and 5 as originally filed.

Claims 17, 18, 26, 27, 28 and 30 have been cancelled, without prejudice.

Claims 2 to 11, 13, 15 to 16, 19 to 22, 24 and 25 have been rewritten in single dependent form.

Claim 14 now depends from any one of claims 1 to 13, 15 to 16 and 19 to 22. Claim 24 now depends from claim 14.

New claim 31 is based upon a combination of original claims 1, 11, 13, 14, 24 and 21. It is noted that all of the original claims were drafted in multiple dependent form, and hence new claim 31 is fully based on these original claims.

New claim 32 is based upon new claim 31, and additionally incorporates the subject matter of Claims 12, 22 and 8.

New claim 33 is based upon claims 2, 13, 14 and 24 and additionally incorporates the preferred definition of R_2 at page 20, line 16 to page 21, line 29, and the preferred definition of Cy at page 13, lines 13 to 21.

New claim 34 is based upon new claim 33 and claim 4.

New claim 35 is based upon new claim 33 and claim 5.

Favorable consideration of the application is requested.

Respectfully submitted,

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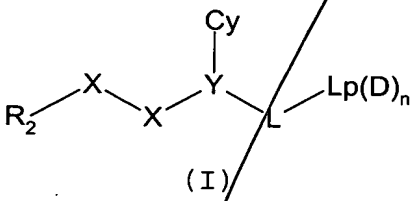
February 1, 2002

Attachments: Abstract on separate sheet
Hand-amended (marked-up) Claims
Clean Pending Claims

Clean Set of Claims

1. A serine protease inhibitor compound of formula (I)



(I)

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen, hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not unsubstituted aminoalkyl;

Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups R_{3a} or $R_{3i}X_i$;

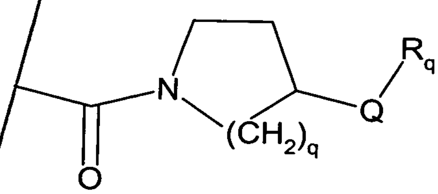
each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy;

X_i is a bond, O, NH or CH_2;

R_{3i} is phenyl, pyridyl or pyrimidinyl optionally substituted by R_{3a}; and

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a},

and $-L-Lp(D)_n$ is of the formula:



wherein:

q is 1 or 2;

Q is -O- or -NH-;

and R_q is R_c which is pyridyl, pyrimidin-4-yl, pyridazin-3-yl, pyridazin-4-yl or phenyl (which phenyl or pyridyl group may bear a fluoro, chloro, alkyl, $CONH_2$, SO_2NH_2, dialkylaminosulphonyl, methoxy, methylthio, alkylsulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, alkoxycarbonyl, acetylamino, cyano, ethoxy, nitro, hydroxy,

alkylsulphonylamino, triazolyl or tetrazolyl substituent);

or a physiologically-tolerable salt thereof.

2. (amended) A serine protease inhibitor compound according to Claim 1

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen, hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not unsubstituted aminoalkyl;

Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

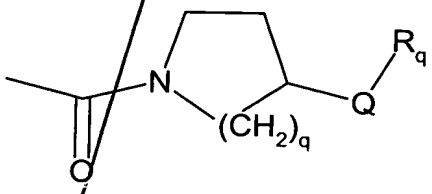
Cy is a saturated or unsaturated, mono or poly cyclic,

homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a};

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl; and

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a},

and $-L-Lp(D)_n$ is of the formula:



wherein:

q is 1 or 2;

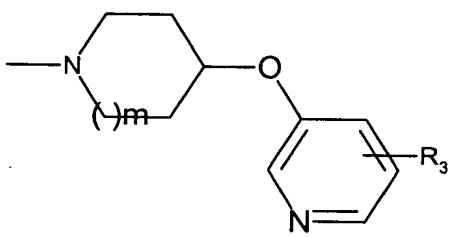
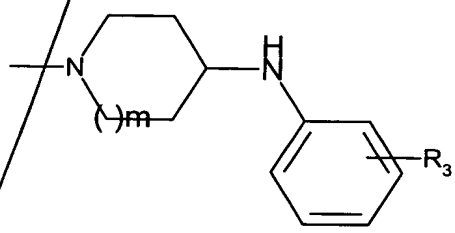
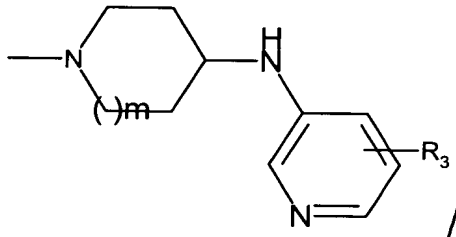
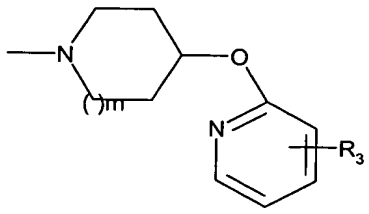
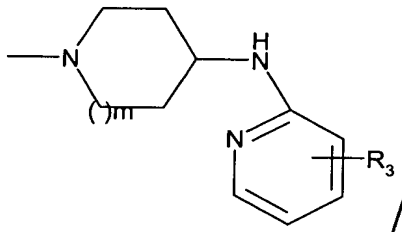
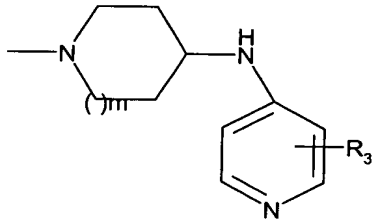
Q is -O- or -NH-;

and R_q is R_c which is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, SO_2NH_2, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent);

or a physiologically-tolerable salt thereof.

3. (amended) A compound according to claim 1 wherein q is 2.

4. (amended) A compound according to claim 2 wherein -Lp(D)n is selected from the following formulae:

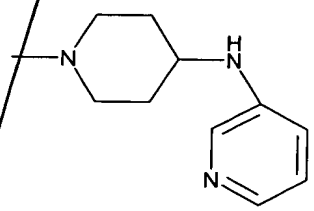
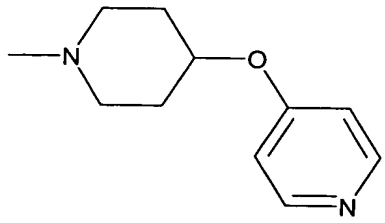







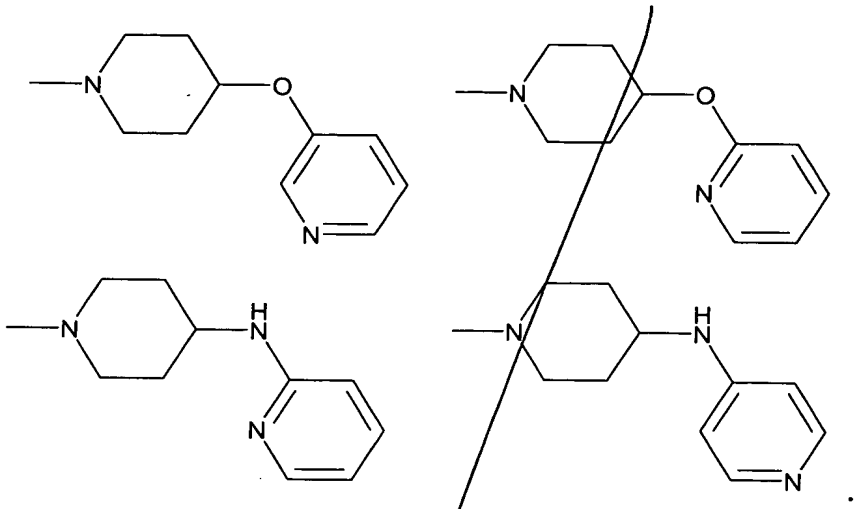
wherein:

m represents 0 or 1; and

when R_3 is present as a substituent on an aromatic ring, it is selected from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxycarbonyl, acetylamino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl.

5. (amended) A compound according to claim 2 wherein -Lp(D)n is selected from the following formulae:



6.(amended) A compound according to claim 1 wherein Q is -NH-.

7.(amended) A compound according claim 1 wherein Rc is pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimid-4-yl or phenyl.

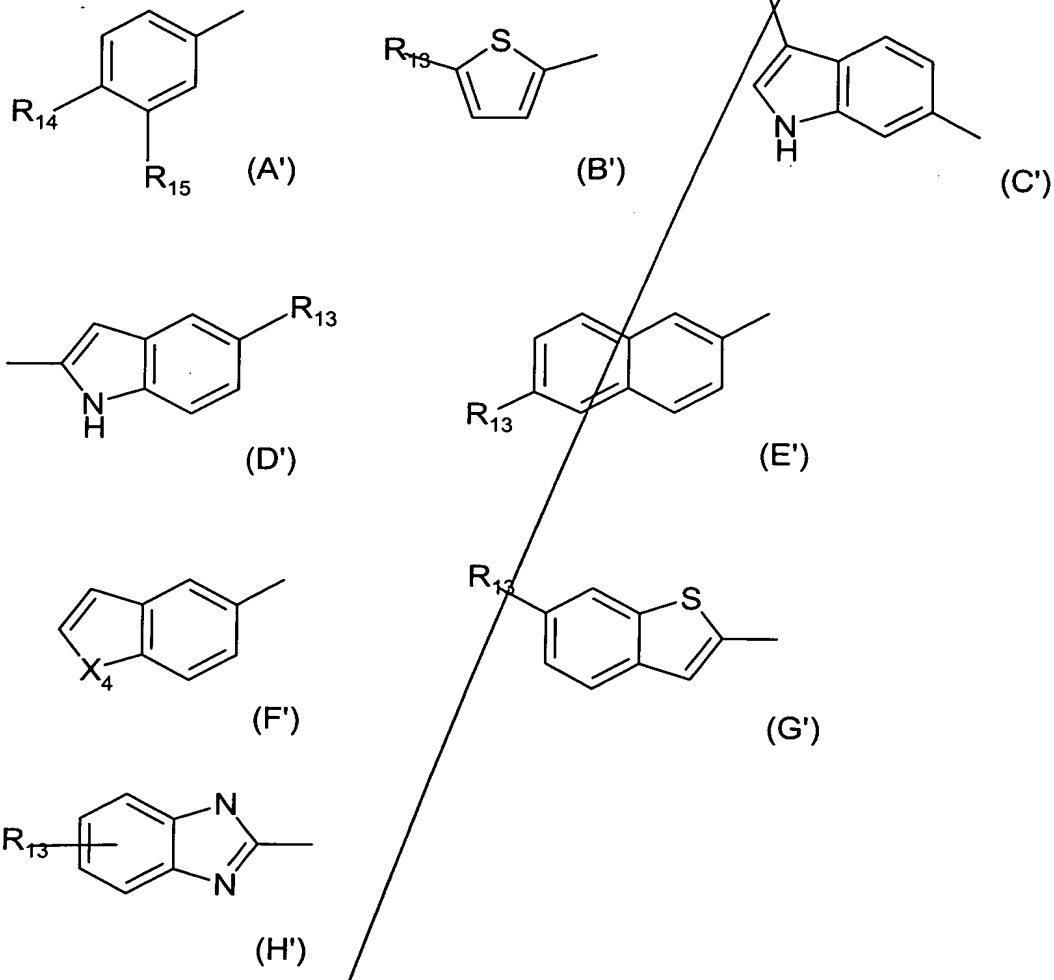
8. (amended) A compound according to claim 1 wherein Rc is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylsulfonylphenyl, 2-methylthiophenyl, pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

9. (amended) A compound according to claim 1 wherein R_2 is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl (each of which is optionally substituted as defined in claim 1).

10. (amended) A compound according to claim 1 wherein optional substituents for R_2 are selected from:
fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy, trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano, trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino, carboxy, acetoxy, hydroxy, methyl, ethyl, amido ($CONH_2$),

aminomethyl, methoxy and ethoxy.

11.(amended) A compound according to claim 1 wherein R_2 is selected from one of the formula (A') to (H'):



wherein X_4 is O or S, R_{13} is selected from hydrogen, chloro or methyl and R_{14} is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen, methyl, fluoro, chloro and amino.

12. A compound according to claim 11, wherein R_2 is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

13. (amended) A compound according to claim 1 wherein -X-X- is -CONH-.

14. (amended) A compound according to any one of claims 1 to 13, 15 to 16 and 19 to 22 wherein Y is CH.

15. (amended) A compound according to claim 1 wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinolyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by $R_{3i}X_i$ in which X_i is a bond, O, NH or CH_2 and R_{3i} is phenyl or pyridyl optionally substituted by R_{3a}.

16. (amended) A compound according to claim 2, wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

17. (cancelled on national phase entry)

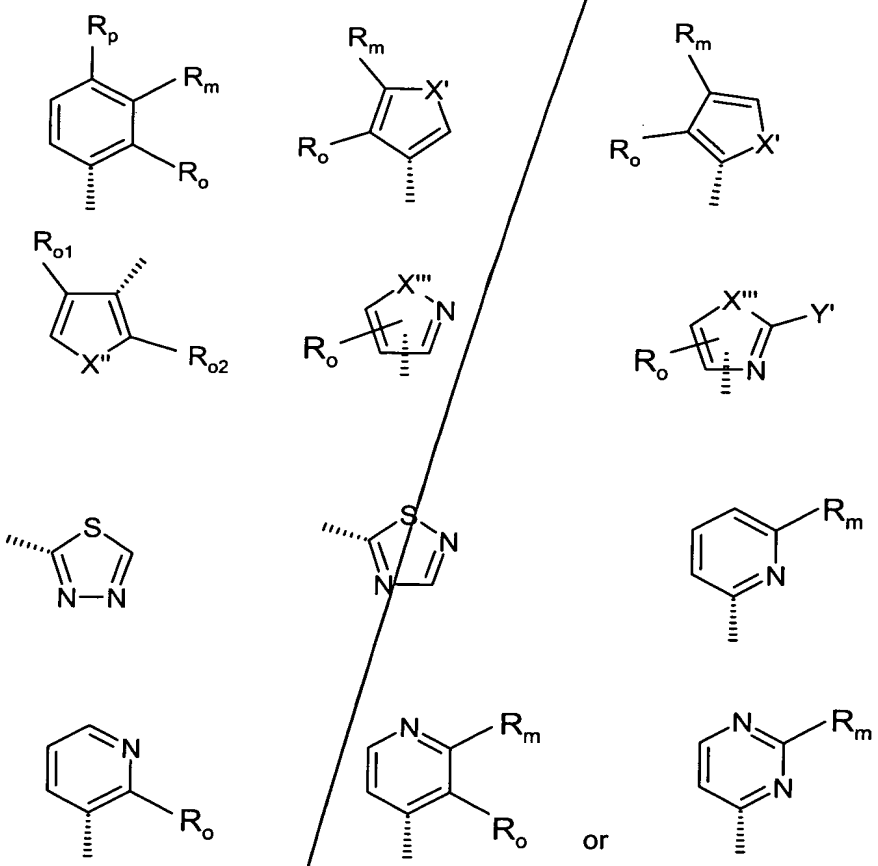
18. (cancelled on national phase entry)

19. (amended) A compound according to claim 1 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl,

methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, bromo, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-1-ylcarbonyl and $-OCH_2O-$ (which is bonded to two adjacent ring atoms in Cy).

20. (amended) A compound according to claim 2 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.

21. (amended) A compound according to claim 1 wherein Cy is selected from:



wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R_o is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl;

R_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S, and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

R_p is selected from hydrogen and fluoro; or

R_o and R_m or R_m and R_p form an -OCH2O- group; or
R_o and R_m together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroary ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and
one of R_{o1} and R_{o2} is hydrogen and the other is R_o.

22. (amended) A compound according to claim 1 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naph-1-thyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl.

23. A compound as claimed in Claim 1, which is selected from 1-(indol-6-carbonyl-D-phenylglycinyl)-4-(4-pyridoxy)-piperidine; 1-[indole-6-carbonyl-D,L-(2-chlorophenyl)glycinyl]-4-(pyridin-4-yloxy)piperidine, and physiologically-tolerable salts thereof.

24. (amended) A compound as claimed in Claim 14, in which the alpha atom in Y is carbon and has the conformation that would result from construction from a D-α-aminoacid NH_2-CR_{1b}(Cy)-COOH where the NH_2 represents part of X-X.

25. (amended) A pharmaceutical composition, which comprises a compound as claimed in Claim 1 together with at least one pharmaceutically acceptable carrier or excipient.

26. (cancelled on national phase entry).

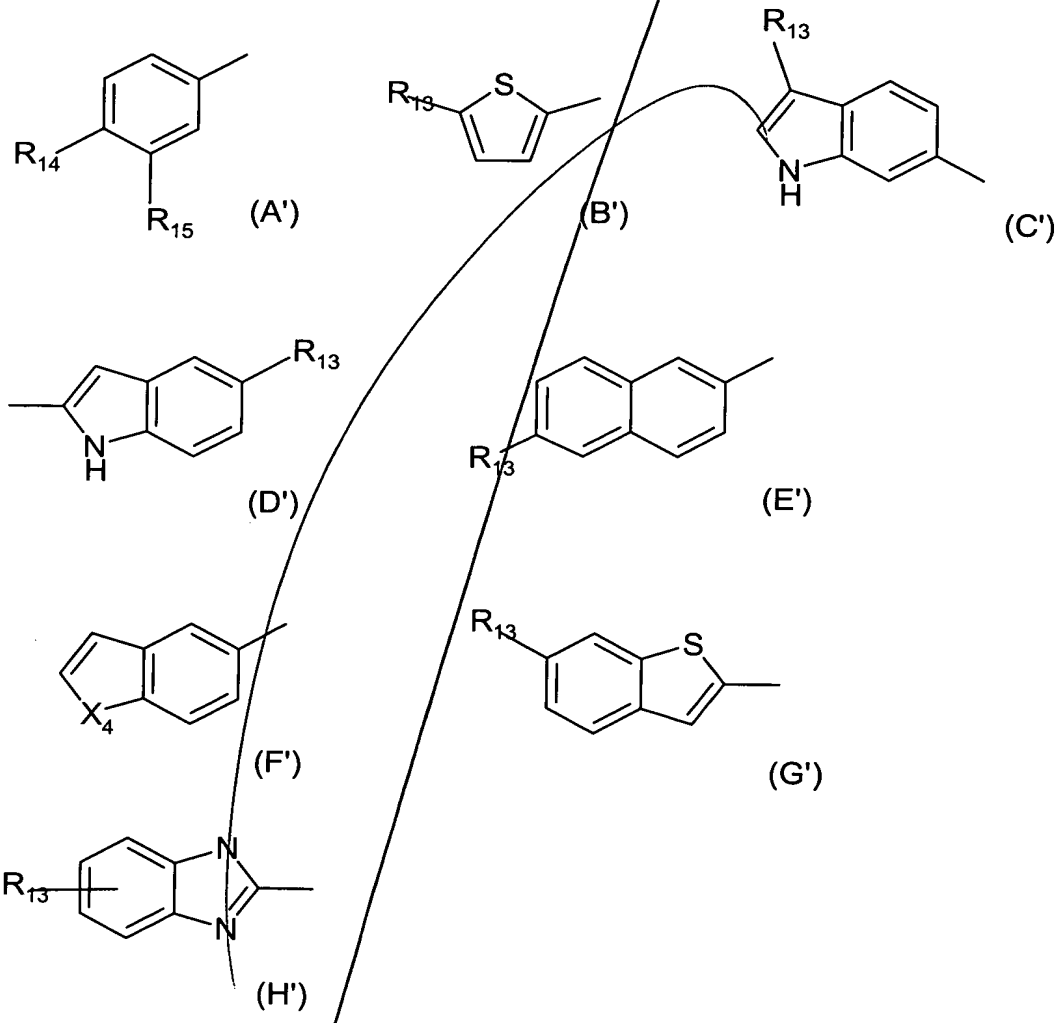
27. (cancelled on national phase entry)

28. (cancelled on national phase entry).

29. A method of treatment of the human or non-human animal body to combat a thrombotic disorder, said method comprising administering to said body an effective amount of a compound according to Claim 1.

30. (cancelled on national phase entry).

31. (new) A compound as claimed in Claim 1, in which R_2 is selected from one of the formula (A') to (H'):



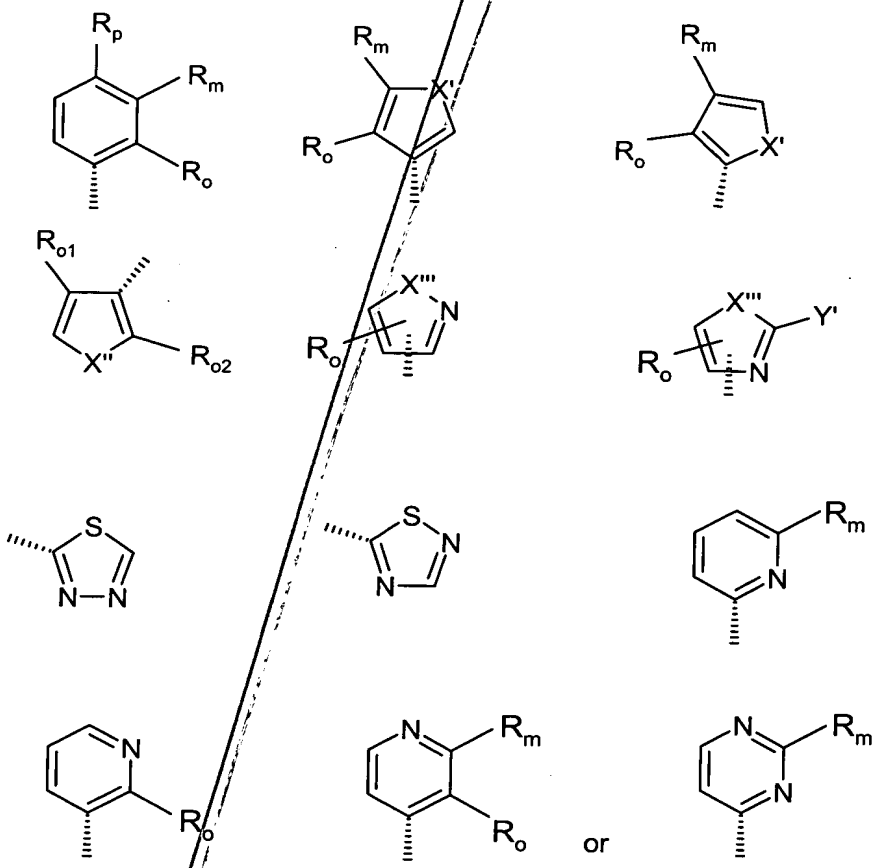
wherein X_4 is O or S, R_{13} is selected from hydrogen, chloro or methyl and R_{14} is selected from hydrogen, methyl,

ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen, methyl, fluoro, chloro and amino;

-X-X- is -CONH-;

Y is CH and has the conformation that would result from construction from a D-α-aminoacid NH_2-CR_{1b}(Cy)-COOH where the NH_2 represents part of X-X; and

Cy is selected from:



wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R_O is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and

methylsulphonyl;

R_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S, and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

R_p is selected from hydrogen and fluoro; or

R_o and R_m or R_m and R_p form an -OCH2O- group; or

R_o and R_m together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroary ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and

one of R_{o1} and R_{o2} is hydrogen and the other is R_o.

32. (new) A compound according to Claim 31, in which

R_2 is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl;

Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naph-1-thyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl; and

Rc is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylsulfonylphenyl, 2-methylthiophenyl, pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

33. (new) A compound according to Claim 2, in which

R_2 represents:

(i) phenyl optionally being substituted in the 3 and/or 4 position by fluoro, chloro, bromo, iodo, nitro,

difluoromethoxy, trifluoromethoxy, amino, cyano, trifluoromethyl, methylthio, vinyl, carboxy, acetoxy, $MeSO_2$-, hydroxy, methoxy, ethoxy, methyl, methoxycarbonyl, methylamino, ethylamino or amido, and optionally substituted at the 6 position by amino, hydroxy, fluoro, methoxycarbonyl, cyano or aminomethyl;

(ii) naphth-2-yl optionally substituted at the 6, position by hydroxy and optionally substituted at the 3 position by amino or hydroxy;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by chloro, bromo, amino, methyl or methoxy;

(iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by methylthio, methyl or acetyl;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl substituted at the 5 position by methyl;

(ix) pyrid-2-yl optionally substituted at the 6 position by chloro;

(x) pyrid-3-yl optionally substituted at the 4 position by chloro;

(xi) benzofur-2-yl optionally substituted at the 3 position by chloro, methyl or methoxy, at the 5 or 6 position by methyl and at the 6 position by methoxy;

(xii) indol-2-yl optionally substituted on the indole nitrogen atom by methyl and optionally substituted at the 5 or 6 position by fluoro, chloro, bromo, methyl or methoxy;

(xiii) indol-6-yl substituted at the 5 position by chloro, fluoro or hydroxy and optionally substituted at the 3 position by chloro or methyl; or

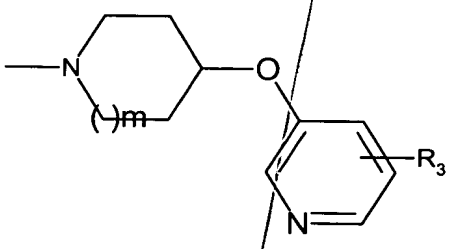
(xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by fluoro, chloro or methyl, and optionally substituted at the 5 or 6 position by fluoro, chloro, methyl, hydroxy, or methoxy;

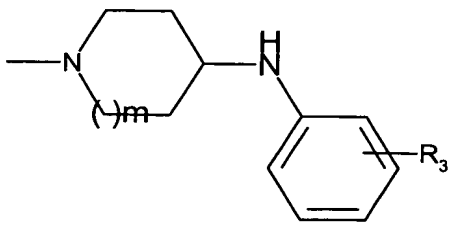
-X-X- is -CONH-;

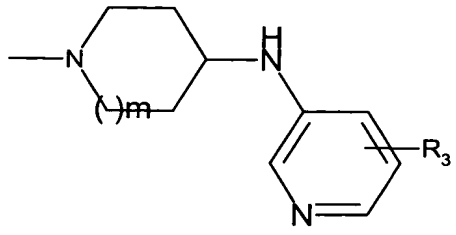
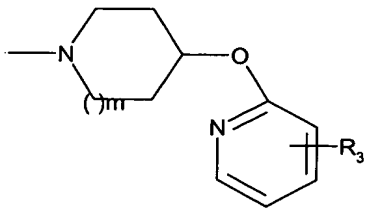
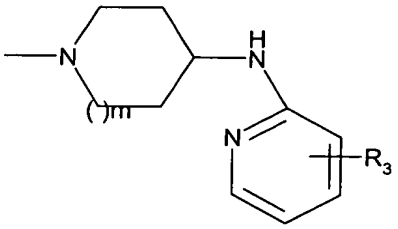
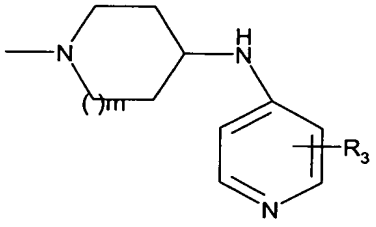
Y is CH and has the conformation that would result from construction from a D-α-aminoacid NH_2-CR_{1b}(Cy)-COOH where the NH_2 represents part of X-X; and

Cy is selected from phenyl, 4-aminophenyl, 4-amidophenyl, 4-(N-methyl)amidophenyl, 4-(N,N-dimethyl)amidophenyl, 2-chlorophenyl, 2-methylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-hydroxphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 4-carboxyphenyl, 3-ethylsulphonylaminophenyl, thien-2-yl, thien-3-yl, thiazol-4-yl, thiazol-5-yl, 2-methylthiazol-4-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, cyclohexyl and naphth-1-yl.

34. (new) A compound according to Claim 33, in which -Lp(D)n is selected from the following formulae:





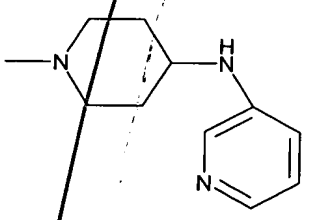
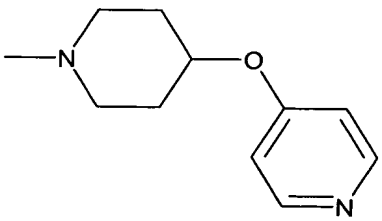
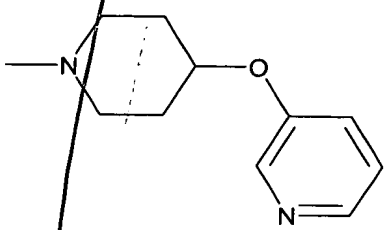
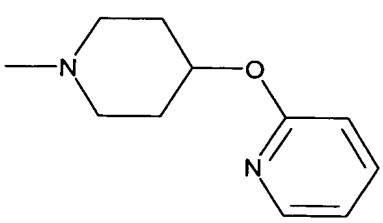





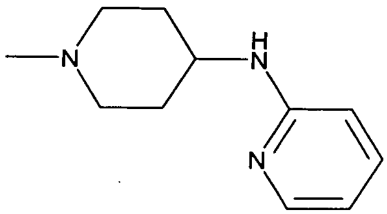
wherein:

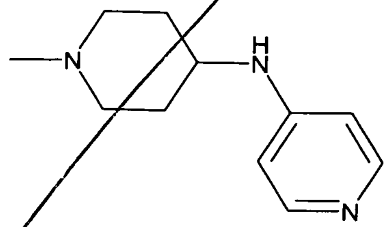
m represents 0 or 1; and

when R_3 is present as a substituent on an aromatic ring, it is selected from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxycarbonyl, acetylamino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl.

35. (new) A compound according to Claim 33, in which -Lp(D)n is selected from the following formulae:





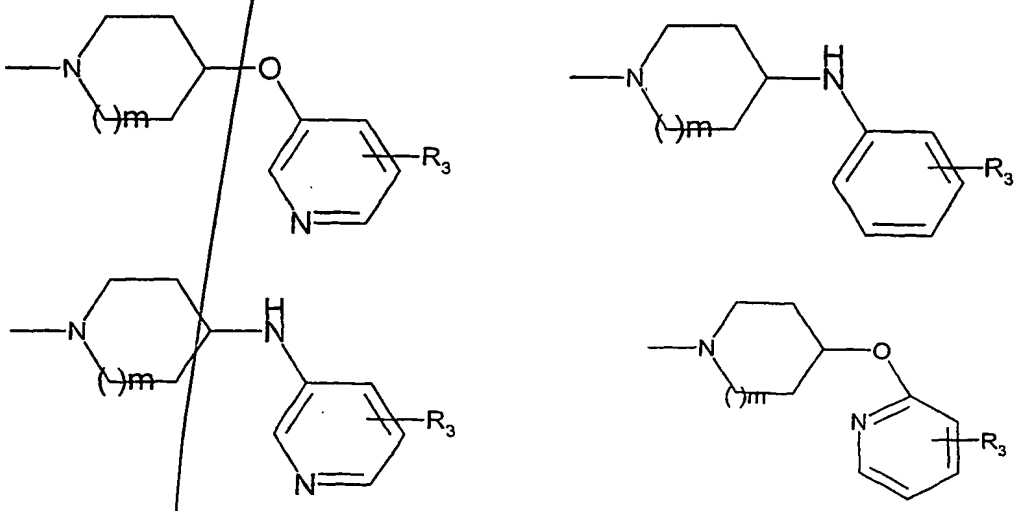
and S; alkyl, alkenyl or alkynyl groups or alkylene moieties preferably contain up to 6 carbons, e.g. C_{1-6} or C_{1-3}; cyclic groups preferably have ring sizes of 3 to 8 atoms; and fused multicyclic groups preferably contain 8 to 16 ring atoms.

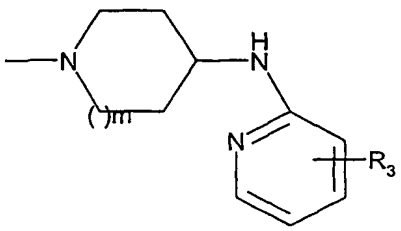
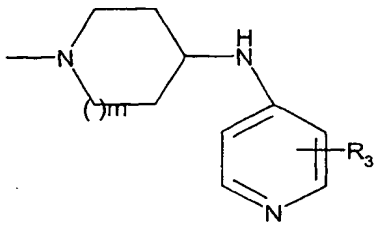
Examples of particular values for R_{1a} are: hydrogen, methyl or ethyl. R_{1a} is preferably a hydrogen atom.

The linker group from the R_2 group to the alpha atom is preferably selected from -CH=CH-, -CONH-, -CONR$_{1a}$-, -NH-CO-, -NH-CH_2-, -CH_2-NH-, -CH_2O-, -OCH_2-, -COO-, -OC=O- and -CH_2CH_2-. Preferably, the X moiety nearest to the alpha atom is an NH or O atom, most preferably a NH group. The X moiety alpha to the aromatic ring is preferably a carbon based group such as CH_2 or CO, preferably CO. Thus a particularly preferred linker X-X is -CONH-. In an alternative embodiment the linker is preferably a -OCH_2- group.

Examples of particular values for R_{1b} are: hydrogen, (1-4C)alkyl, such as methyl or hydroxy(1-4C)alkyl, such as hydroxymethyl. R_{1b} is preferably a hydrogen atom.
The alpha atom (Y) is preferably a CH or C(CH_3) group, especially CH.

Preferably, the group Lp(D)$_n$ is selected from the following formulae:



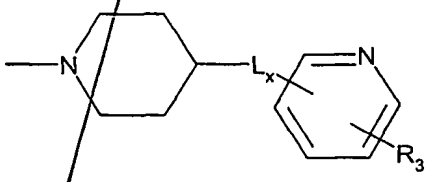



wherein:

m represents 0 or 1; and

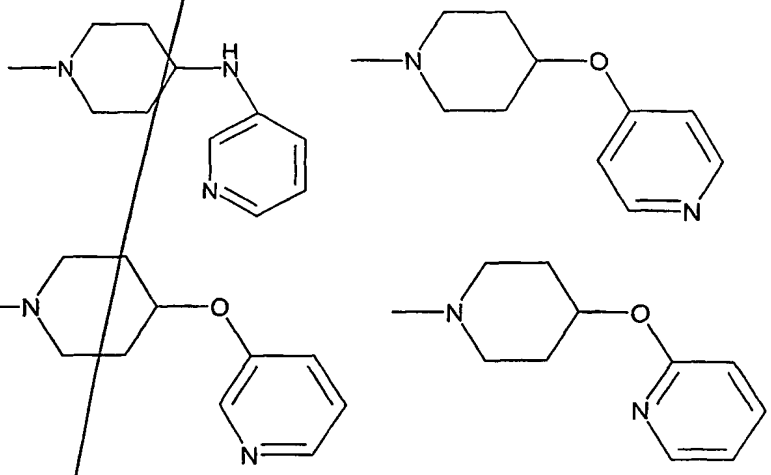
when R_3 is present as a substituent on an aromatic ring, it is selected from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxycarbonyl, acetylamino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl.

One group of formula $Lp(D)_n$ is that of formula



in which L_X represents O or NH.

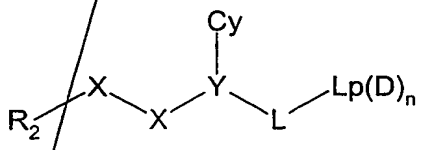
For example specific groups of formula $Lp(D)_n$ include the following formulae:



Hand amended claims

Claims

1. A serine protease inhibitor compound of formula (I)



(I)

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen, hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not unsubstituted aminoalkyl;

Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups R_{3a} or $R_{3i}X_i$;

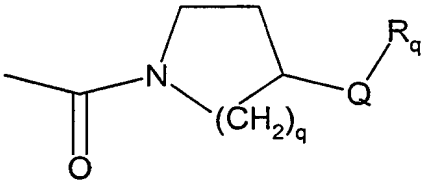
each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy;

X_i is a bond, O, NH or CH_2;

R_{3i} is phenyl, pyridyl or pyrimidinyl optionally substituted by R_{3a}; and

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a},

and $-L-Lp(D)_n$ is of the formula:



wherein:

q is 1 or 2;

Q is -O- or -NH-;

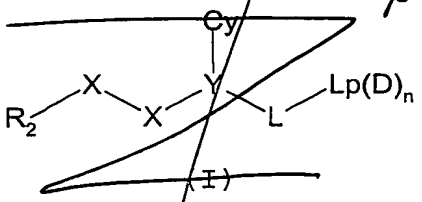
and R_q is R_c which is pyridyl, pyrimidin-4-yl, pyridazin-3-yl, pyridazin-4-yl or phenyl (which phenyl or pyridyl group may bear a fluoro, chloro, alkyl, $CONH_2$, SO_2NH_2, dialkylaminosulphonyl, methoxy, methylthio, alkylsulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, alkoxycarbonyl, acetylamino, cyano, ethoxy, nitro, hydroxy,

alkylsulphonylamino, triazolyl or tetrazolyl substituent);

or a physiologically-tolerable salt thereof.

(amended) according to claim 1

2. A serine protease inhibitor compound ~~of formula (I)~~



~~(I)~~

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen, hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not

unsubstituted aminoalkyl;

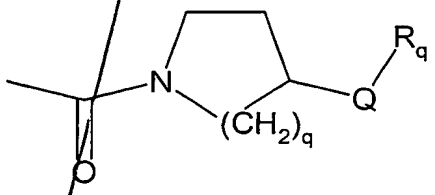
Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a};

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl; and

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a},

and -L-$Lp(D)_n$ is of the formula:



wherein:

q is 1 or 2;

Q is -O- or -NH-;

and R_q is R_c which is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, SO_2NH_2, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent);

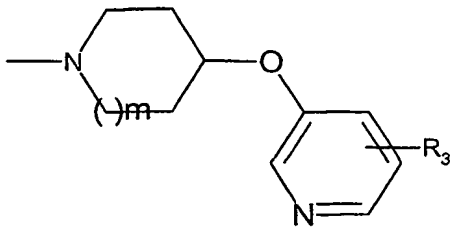
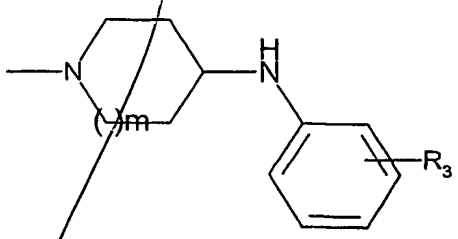
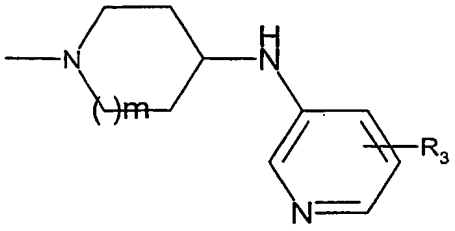
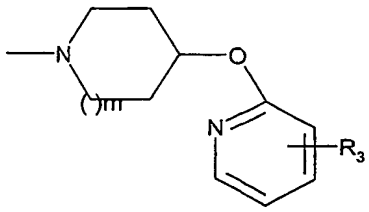
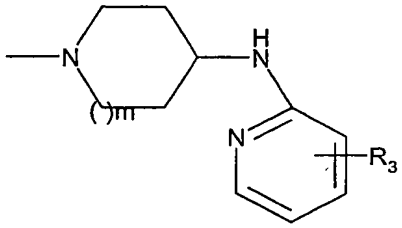
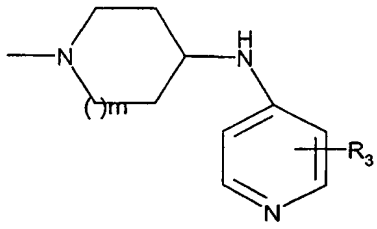
or a physiologically-tolerable salt thereof.

(amended)

3. A compound according to ~~either~~ claim 1 ~~or claim~~ 2 wherein q is 2.

(amended)

4. A compound according to ~~any of~~ claims 2 ~~1 to 3~~ wherein -Lp(D)n is selected from the following formulae:

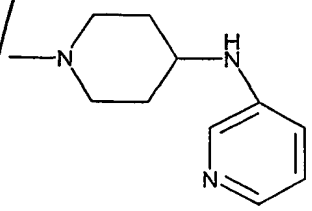
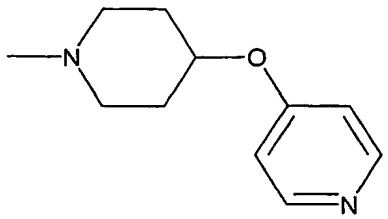
wherein:

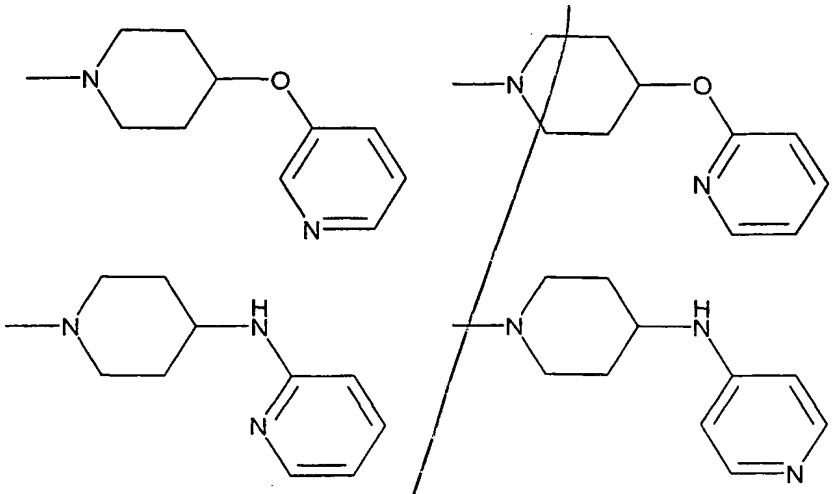
m represents 0 or 1; and

when R_3 is present as a substituent on an aromatic ring, it is selected from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxycarbonyl, acetylamino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl.

(amended)

5. A compound according to ~~any of~~ claim~~s~~ ~~1 to 3~~ 2 wherein - Lp(D)n is selected from the following formulae:



(amended)

6. A compound according to ~~any one of~~ claims 1 ~~to 5~~ wherein Q is -NH-.

(amended)

7. A compound according to ~~any of~~ claims 1 ~~to 3~~ wherein Rc is pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimid-4-yl or phenyl.

(amended)

8. A compound according to ~~any of~~ claims 1 ~~to 3~~ wherein Rc is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylsulfonylphenyl, 2-methylthiophenyl, pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

(amended)

9. A compound according to ~~any one of~~ claims 1 ~~to 8~~ wherein R_2 is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl (each of which is optionally substituted as defined in claim 1).

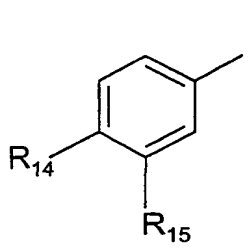
(amended)

10. A compound according to ~~any one of~~ claims 1 ~~to 9~~ wherein optional substituents for R_2 are selected from: fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy, trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano, trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino,

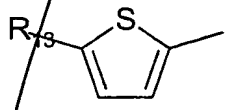
carboxy, acetoxy, hydroxy, methyl, ethyl, amido ($CONH_2$), aminomethyl, methoxy and ethoxy.

(amended)

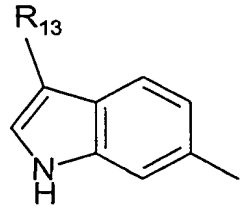
11. A compound according to ~~any one of~~ claims 1 ~~to 10~~ wherein R_2 is selected from one of the formula (A') to (H'):



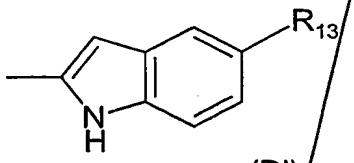
(A')



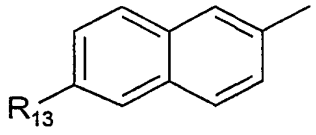
(B')



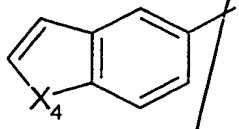
(C')



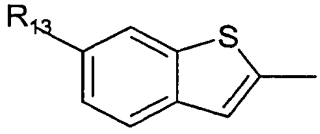
(D')



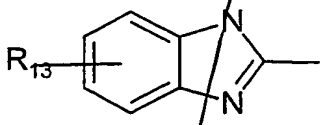
(E')



(F')



(G')



(H')

wherein X_4 is O or S, R_{13} is selected from hydrogen, chloro or methyl and R_{14} is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen, methyl, fluoro, chloro and amino.

12. A compound according to claim 11, wherein R_2 is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

(amended)

13. A compound according to ~~any one of~~ claims 1 ~~to 12~~ wherein -X-X- is -CONH-.

(amended)

14. A compound according to ~~any one of claims 1 to 13~~ any one of claim 1 to 12, 15 to 16 and 19 to 22 wherein Y is CH.

(amended)

15. A compound according to ~~any one of~~ claims 1 ~~to 14~~ wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinolyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by $R_{3i}X_i$ in which X_i is a bond, O, NH or CH_2 and R_{3i} is phenyl or pyridyl optionally substituted by R_{3a}.

(amended)

16. A compound according to ~~any one of~~ claims 2 ~~1 to 14~~, wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

(cancelled on national phase entry)

17. ~~A compound according to any one of claims 1 to 16~~ wherein R_{3a} is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, ~~alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a~~

~~group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S;~~ and R^{11} and R^{12} are independently selected ~~from~~ hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino ~~group~~) and $-OCH_2O-$ which is bonded to two adjacent ~~ring atoms in Cy~~.

(cancelled on national phase entry)

18. ~~A compound according to any one of claims 1 to 16 wherein~~ R_{3a} is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, ~~alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl~~.

(amended)

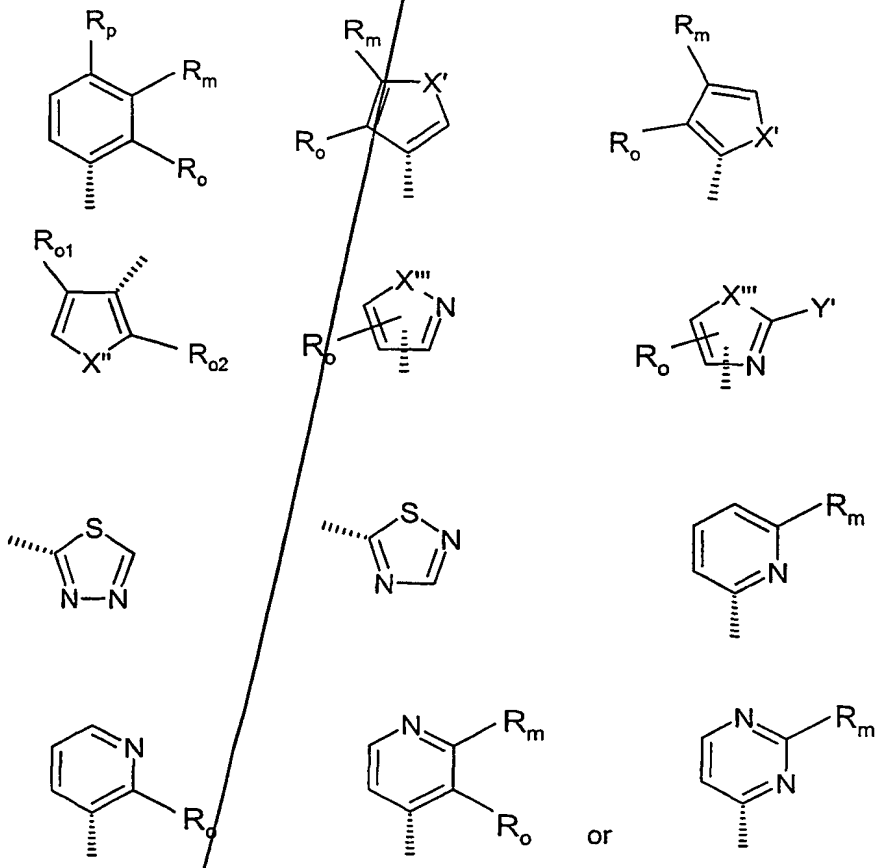
19. A compound according to ~~any one of~~ claims 1 ~~to 16~~ wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, bromo, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-1-ylcarbonyl and $-OCH_2O-$ (which is bonded to two adjacent ring atoms in Cy).

(amended)

20. A compound according to ~~any one of~~ claims 2 ~~1 to 16~~ wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.

(amended)

21. A compound according to ~~any one of~~ claims 1 ~~to 16~~ wherein Cy is selected from:



wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

X'" is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R_o is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl;

R_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S, and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

R_p is selected from hydrogen and fluoro; or

R_o and R_m or R_m and R_p form an -OCH2O- group; or

R_o and R_m together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroary ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and

one of R_{o1} and R_{o2} is hydrogen and the other is R_o.

(amended)

22. A compound according to ~~any one of~~ claims 1 ~~to 16~~ wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naph-1-thyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl.

23. A compound as claimed in Claim 1, which is selected from 1-(indol-6-carbonyl-D-phenylglycinyl)-4-(4-pyridoxy)-

piperidine; 1-[indole-6-carbonyl-D,L-(2-chlorophenyl)glycinyl]-4-(pyridin-4-yloxy)piperidine, and physiologically-tolerable salts thereof.

(amended)

24. A compound as claimed in ~~any one of~~ Claims ~~1 to 23~~ 14, in which the alpha atom in Y is carbon and has the conformation that would result from construction from a D-α-aminoacid NH_2-CR_{1b}(Cy)-COOH where the NH_2 represents part of X-X.

(amended)

25. A pharmaceutical composition which comprises a compound as claimed in ~~any one of~~ Claims 1 ~~to 24~~ together with at least one pharmaceutically acceptable carrier or excipient.

(cancelled on national phase entry)

26. A compound as claimed in any one of Claims 1 to 24 for use in therapy.

(cancelled on national phase entry)

27. ~~Use of a serine protease inhibitor according to any one of Claims 1 to 24 for the manufacture of a medicament for the treatment of a thrombotic disorder.~~

(cancelled on national phase entry)

28. ~~A pharmaceutical composition, which comprises a compound as claimed in any one of Claims 1 to 24 together with at least one pharmaceutically acceptable carrier or excipient for use in the treatment of a thrombotic disorder~~.

29. A method of treatment of the human or non-human animal body to combat a thrombotic disorder, said method comprising administering to said body an effective amount of a compound according to Claim 1.

(cancelled on national phase entry)

30. ~~A compound of formula I as claimed in Claim 1 and named in any one of the Examples herein, or a physiologially acceptable salt thereof~~.

Add new claim 31 to 35